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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/824,593	04/15/2004	Raymond Pratt	109536.159WO1	6645

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EXAMINER	
CHANNAVAJJALA, LAKSHMI SARADA	
ART UNIT	PAPER NUMBER
1611	
MAIL DATE	DELIVERY MODE
02/04/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/824,593	PRATT ET AL.	
	Examiner	Art Unit	
	Lakshmi S. Channavajjala	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt of response dated 11-17-08 is acknowledged.

Claims 25-45 are pending in the instant application.

Examiner regrets the misidentification of Kish et al (cited on PTO-892 and explanation of the reference in the body of the rejection) as Nath in the statute. However, as it is evident from the rejection and PTO-892, the rejection employed the teachings of Kish et al and not Nath.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 25-45 are rejected less than 35 U.S.C. 103(a) as being unpatentable over WO 98/39000 (WO) in view of US 5,278,176 to Lin and Kish et al.

WO teaches methods of treating disorders of attention or improving attention by administering an effective amount of a cholinesterase inhibitor. WO teaches that acetylcholine is a neural transmitter for transmitting messages across the synapse to a cholinergic message by stimulating the cholinergic receptor for neuronal messages such as memory (page 3, L 23-29). WO teaches that cholinesterase rapidly destroys acetylcholine resulting in a weak cholinergic stimulation, experienced as a memory loss, and states that one way to overcome the above loss is to interfere with the ability of cholinesterase to degrade acetylcholine, as by treatment with cholinesterase inhibitors (page 4, l 5-12). WO teaches all of the instant claimed compounds, including donepezil, for their cholinesterase inhibiting activity and thus inhibiting memory loss (pages 5+).

WO fails to teach the claimed method of treating substance abuse or treating withdrawal symptoms or decreasing the rate of relapse.

Lin teaches selective and potent nicotinic agonists that are useful in treating dementias, attention disorders, and anxiety associated with cognitive impairment or substance abuse withdrawal characterized by decreased cholinergic function (abstract). Lin teaches that chronic alcoholism (reads on instant substance abuse, see instant claim 25) and the resultant brain disease such as Alzheimer's disease, is characterized by diffuse reductions in cortical cerebral blood flow in those brain regions where cholinergic neurons arise (col. 2, L 61-65). Lin further states that nicotine withdrawal syndrome associated with tobacco use is characterized by craving for nicotine, irritability, frustration, anger, difficulty in concentration etc (col. 4, L 60-67). Lin suggests that symptoms associated with withdrawal of nicotine or compounds that act as nicotine agonists for acetylcholine receptors can alleviate other addictive substances.

Kish (abstract only) teaches Cognitive impairment has been reported in some chronic users of psychostimulants, raising the possibility that long-term drug exposure might damage brain neuronal systems, including the cholinergic system which is responsible for normal cognition. Kish reports that a measurement of the activity of choline acetyltransferase (ChAT), the marker enzyme for cholinergic neurons, in autopsied brain of chronic users of cocaine, methamphetamine, and, for comparison, heroin showed that as compared with the controls, mean ChAT levels were normal in all cortical and sub cortical brain areas examined. However, the two of 12

methamphetamine users, who had the highest brain/blood drug levels at autopsy, had a severe (up to 94%) depletion of ChAT activity in cerebral cortex, striatum, and thalamus. Based on the subjects examined in the present study, our neurochemical data, Kish states that the brain cholinergic neurone damage is unlikely to be a typical feature of chronic use of cocaine, methamphetamine, or heroin, but that exposure to very high doses of methamphetamine could impair, at least acutely, cognitive function requiring a normal nucleus basalis cholinergic neuronal system. Reduced brain ChAT might be explained in part by a hyperthermia-related mechanism as low ChAT levels have also been observed in brain of some patients with neuroleptic drug-associated hyperthermia. Studies of cognitive and brain cholinergic status in high dose users of MA are warranted. Kish does not teach donepezil for cognitive impairment or cholinergic status.

It would have been obvious for one of an ordinary skill in the art at the time of the instant invention to use the cholinesterase inhibitors such as donepezil and other compounds of treating substance abuse or withdrawal symptoms associated with substance abuse because both Lin and Kish emphasizes that the cholinergic system plays a profound role in substance abuse or drug withdrawal symptoms that are associated with substances such as alcohol, cocaine or methamphetamine (which are claimed to cause substance abuse) and Lin states that cholinesterase inhibitors effectively interfere with and alleviate the substance abuse and the associated withdrawal symptoms. Even though Kish states that high doses of drugs impair cognitive functioning requiring a normal cholinergic neuronal system, instant claims are

silent regarding the amount of substances that cause the withdrawal symptoms or symptoms of substance abuse. Hence, one of an ordinary skill in the art would have expected the cholinesterase inhibitors of WO to be effective in reducing the substance abuse or in interfering with the drug withdrawal symptoms caused by abusive drugs such as nicotine, cocaine, methamphetamine, alcohol etc.

While Lin does not teach al of the claimed drugs that result in the abuse or cause the withdrawal symptoms, Lin teaches the underlying mechanism that results in the claimed abuse and its withdrawal symptoms and hence a skilled artisan would have expected to effectively reduce substance abuse, caused by any substance, with the cholinesterase inhibitors of WO. Further, optimizing the amount and the route of administration of the compounds of WO, so as to reduce substance addiction and also prevent the return to drug seeking behavior would have been within the scope of a skilled artisan.

Response to Arguments

Upon further consideration, the following rejection is withdrawn

Claims 25-45 are rejected less than 35 U.S.C. 103(a) as being unpatentable over WO 98/39000 (WO) in view of Kish et al.

The only rejection present in the application is:

Claims 25-45 are rejected less than 35 U.S.C. 103(a) as being unpatentable over WO 98/39000 (WO) in view of US 5,278,176 to Lin and Kish et al.

Applicant's arguments filed 11-17-08 have been fully considered but they are not persuasive. Applicants argument that WO reference does not disclose or suggest the

claimed method of treating substance abuse in a patient in need thereof comprising administering a therapeutically effective amount of donepezil or a pharmaceutically acceptable salt thereof is not persuasive because the rejection acknowledged that WO teaches the claimed compounds for treating disorders of attention and for improving attention but not the claimed method. Examiner relied on the teachings of Lin and Nath for the suggestion to employ the compounds of WO for instant method. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

With respect to Lin reference, it is argued that Lin does not cure the deficiencies of WO 98/39000 to disclose the presently claimed invention because Lin is directed to compounds that are nicotinic agonists *(see* Lin at Abstract; column 1, lines 5-8; column 6, lines 58-60; column 21, lines 58 to column 22, line 25; column 22, lines 55-62), as opposed to instant application that is directed to the use of compounds that are cholinesterase antagonists (i.e., cholinesterase inhibitors). It is further argued that Lin's compounds are structurally unrelated to the claimed compounds (i.e., donepezil, compounds of Formula (I)) and hence there is no teaching or suggestion in Lin which would lead one of skill in the art to conclude that the nicotine derivative agonists described therein may be substituted with the cholinesterase antagonists of the instant claims. Lin in combination with WO 98/39000 does not render the claimed invention obvious. Withdrawal of this portion of the rejection is respectfully requested. Applicants'

arguments are not persuasive because the teachings of Lin are relied upon not for the claimed compounds but for the teaching that the symptoms associated with withdrawal of nicotine or compounds that act as nicotine agonists for acetylcholine receptors can alleviate other addictive substances. A skilled artisan reading the disclosure of Lin would recognize that substance abuse such as chronic alcoholism (or even tobacco products, see col. 1, L 15-20 & col. 4, L 61-col. 5, L 49) is characterized by diffuse reductions in cortical cerebral blood flow in those brain regions where cholinergic neurons arise and reduces the cholinergic function by substantial reduction of cholinergic receptors. Lin also states that the degeneration of cholinergic neurotransmitter system causes a decrease in cortical functions and is important particularly in effect of alcohol in cholinergic system. Thus, it would have been obvious for one skilled in the art to employ compounds or active agents that inhibit the reduction in cholinergic function or alleviation of cholinergic function so as to improve the cognitive functions associated with substance abuse. WO teaches compounds that inhibit cholinesterase and thus improve the cholinergic stimulation and thus treat attention disorders. Therefore, a skilled artisan would have employed the compounds of WO i.e., cholinesterase inhibitors for treating the impaired cognitive functions due to substance abuse such as alcoholism or tobacco (suggested by Lin).

Examiner explained about the erroneous mistake in identifying the teachings of Kish et al as Nath, which is regretted. It is evident from the rejection and also PTO-892, the rejection only employed the teachings of Kish et al and not that of Nath.

Applicants argue that because the Kish reference suggests that the studies of cognitive and brain cholinergic status in high dose users is of MA is warranted, a conclusion is speculative and based on small cohort of research subjects. It is argued that that reduced choline acetyltransferase activity found occasionally in the brains of methamphetamine users (if even validated by further research) would not suggest to a person of ordinary skill in the art the conclusion that cholinesterase inhibitors be administered for the treatment of substance abuse, particularly that cholinesterase inhibitors are not mentioned in the cited abstract. The above arguments are not persuasive because the reference of Kish provides further substantiates that cholinergic impairment plays a role in brain cognitive functions in addition to what is taught by Lin. While Kish teaches in a particular cohort, instant patient population is not limited to one cohort or does not exclude the cohort of Kish. The mere fact that further studies are warranted according to Kish does not negate the role of cholinergic receptors in cognitive function in psychostimulants. A person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely that product [was] not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103." KSR International Co. v. Teleflex Inc., 550 U.S. ___, ___, 82 USPQ2d 1385, 1397 (2007).

Conclusion

1. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakshmi S. Channavajjala whose telephone number is 571-272-0591. The examiner can normally be reached on 9.00 AM -5.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila G. Landau can be reached on 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lakshmi S Channavajjala/
Primary Examiner,
Art Unit 1611
February 2, 2009